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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,421	09/18/2003	Berndt B. Bruegger	9793-138	1525

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EXAMINER	
WALLENHORST, MAUREEN	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 05/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,421	BRUEGGER, BERNDT B.	
	Examiner	Art Unit	
	Maureen M. Wallenhorst	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-18-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claim 30 is rejected under 35 U.S.C. 102(b) as being anticipated by CA 1,250,213 (submitted in the Information Disclosure Statement filed on September 18, 2003).

CA 1,250,213 teaches of a reagent for use in performing an activated partial thromboplastin time test (APTT) on a blood sample, which comprises a phospholipid and an activator. The activator can be a sulfatide or a mixture of sulfatides. The reagent comprises a 1:1 ratio of the phospholipid (i.e. a phosphatide) and the sulfatide. See the example on page 10 of CA 1,250,213. The reagent also comprises a buffer, and can be freeze-dried. Since CA 1,250,213 teaches the same weight ratio of sulfatide to phosphatide as recited in instant claim 30, the reagent taught by CA 1,250,213 would inherently perform the same function of determining heparin treatment effectiveness, especially when a patient's heparin level is 0 U/ml, which is a possible heparin level recited in claim 30. The situation when a patient's heparin level is 0 U/ml is equivalent to the APTT clotting test taught by CA 1,250,213 on blood samples not having heparin therein.

3. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Bader et al (abstract, submitted in the Information Disclosure Statement filed on September 18, 2003).

Bader et al teach of a reagent comprising recombinant human tissue factor and synthetic phospholipids (i.e. phosphatidyl choline and phosphatidyl serine). Therefore, the reagent taught by Bader et al comprises tissue factor and at least one co-factor selected from the group

consisting of a phosphatide (i.e. the synthetic phospholipids) and a sulfatide. The reagent taught by Bader et al can inherently be used to determine the effectiveness of heparin therapy in a patient by measuring clotting time, as recited in instant claim 16, since the reagent taught by Bader et al is for the determination of prothrombin clotting time in blood samples and claim 16 does not recite a concentration of heparin in the patient's blood, thus allowing the possibility that no heparin is present in the patient's blood, which is equivalent to the determination of clotting time in regular blood samples containing no heparin, as taught by Bader et al.

4. Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Gailani et al (submitted in the Information Disclosure Statement filed on September 18, 2003).

Gailani et al teach of a method and a reagent used to determine the clotting time of a blood sample. In the method, a blood sample is combined with tissue factor, and then clot formation is initiated by the addition of calcium chloride in a 1:10 dilution of rabbit brain cephalin with 1 mmol/L of a bovine brain sulfatide. Rabbit brain cephalin is a type of a phosphatide since it is a phospholipid (i.e. phosphatidylethanolamine). Therefore, the reagent combined with the blood sample in the method of Gailani et al comprises tissue factor, a phosphatide and a sulfatide. See the second column on page 814 of Gailani et al. The reagent taught by Gailani et al can inherently be used to determine the effectiveness of heparin therapy in a patient by measuring clotting time, as recited in instant claims 1 and 16, since the reagent taught by Gailani et al is for the determination of clotting time in blood samples, and claim 1 recites that the heparin concentration in the patient's blood can be "up to 6 U/ml" which could be interpreted to mean a concentration of 0 U/ml, while claim 16 does not recite a concentration of heparin in the patient's blood, thus allowing the possibility that no heparin is present in the

patient's blood. Both situations included within the scope of claims 1 and 16 are equivalent to the determination of clotting time in regular blood samples containing no heparin, as taught by Gailani et al.

5. Claims 16 and 33-34 are rejected under 35 U.S.C. 102(b) as being anticipated by Griffin et al (WO 96/15457, submitted in the Information Disclosure Statement filed on September 18, 2003).

Griffin et al teach of a method for the diagnosis of thrombotic disorders, wherein the clotting time of a test sample of blood is analyzed in the presence and absence of activated protein C (APC). The method is based upon a procoagulant reagent-dependent factor V coagulation assay. The procoagulant reagent refers to any type of reagent that serves as an activator of the intrinsic coagulation pathway. The procoagulant includes activators such as kallikrein and APTT reagent (i.e. a reagent containing a phospholipid and a contact activator such as a sulfatide). Griffin et al teach that the procoagulant is preferably a tissue factor, either from bovine brain or recombinant. The tissue factor may intrinsically include phospholipid or phospholipid may be exogenously included in the test sample. Any type of procoagulant phospholipid can be used. See page 8 of Griffin et al. Griffin et al use the procoagulant reagent to test plasma samples containing heparin in a final concentration of 0.5 U/ml. See example 4 on page 18 of Griffin et al. Therefore, Griffin et al teach of a method and reagent for determining the clotting time in blood samples containing heparin in a low dose by combining the blood sample with a reagent containing tissue factor and a phosphatide. Griffin et al also inherently teach of a reagent comprising tissue factor and a cofactor, wherein when an effective amount of the reagent is contacted with a blood sample having a heparin level between 0 and 6 U/ml, a

predetermined degree of clotting is reached in less than 300 seconds, since the reagent taught by Griffin et al (i.e. a tissue factor and a phosphatide) is the same as in the instant invention which performs this function, and the blood sample in Griffin et al whose clotting time is measured contains a heparin level of 0.5 U/ml, which is included in the scope of instant claim 16 that does not recite a specific concentration of heparin in the patient's blood, and in the scope of instant claims 33-34 that recite a heparin concentration in the patient's blood between 0 and 6 U/ml.

6. Claim 30 is rejected under 35 U.S.C. 102(b) as being anticipated by McDonald et al (US Patent no. 5,039,617, submitted in the Information Disclosure Statement filed on September 18, 2003)

McDonald et al teach of a capillary flow device, method and reagent for measuring activated partial thromboplastin time (APTT). The reagent used comprises a mixture of an activating agent for APTT measurements, usually a bovine sulfatide, and phospholipids such as phospholipid extracts of mammalian brain (i.e. a phosphatide). The two components of the reagent are usually present in proportions such that when using a sulfatide as the activator, the activator is typically present at 0.1 to 1 times the weight amount of the phospholipid, and preferably about 0.5 times the weight amount of the phospholipid. See lines 17-61 in column 10 of McDonald et al. The test is used to measure APTT for blood samples containing a heparin concentration of about 0.1 U/ml and 0.3 U/ml. See example 3 in column 16 of McDonald et al. McDonald et al also teach that other components may be present in the reagent, such as a buffer and stabilizing agents. The device containing the reagent and used to perform the method is described on lines 40-68 of column 13 and lines 1-26 of column 14 in McDonald et al. See also Figures 1A and 1B. The device comprises an inlet port, a first capillary unit connecting the inlet

port to a chamber unit, a second capillary unit for connecting the chamber unit to an exit port, and an exit port. The reagent composition is present in the capillary pathway so as to become dissolved in and mixed with a blood sample applied to the device. Therefore, McDonald et al teach of a reagent composition containing therein a sulfatide and a phosphatide in a weight ratio of 1:1 or 1:2. Since McDonald et al teach the same weight ratio of sulfatide to phosphatide as recited in instant claim 30, the reagent taught by McDonald et al would inherently perform the same function of determining heparin treatment effectiveness in patients having blood heparin levels of between 0-6 U/ml, since McDonald et al teach of the use of the reagent for the determination of clotting time in blood samples containing some level of heparin therein which is greater than 0, i.e. a heparin level of 0.1 U/ml or 0.3 U/ml.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claims 2-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gailani et al. For a teaching of Gailani et al, see previous paragraphs in this Office action.

Gailani et al fail to teach of the concentration levels of the tissue factor and sulfatide in the clotting reagent, fail to teach of freeze-drying the reagent, and fail to teach of the addition of buffers and stabilizing agents to the reagent. However, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to vary the concentration levels of the tissue factor and sulfatide in the reagent taught by Gailani et al to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed. It also would have been obvious to one of ordinary skill in the art to freeze-dry the reagent and add a buffer and stabilizing agents to the reagent taught by Gailani et al in order to preserve the reagent for an extended shelf life.

10. Claims 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffin et al. For a teaching of Griffin et al, see previous paragraphs in this Office action.

Griffin et al fail to teach of the concentration levels of the tissue factor and phosphatide in the procoagulant reagent, fail to teach of freeze-drying the reagent, and fail to teach of the addition of buffers and stabilizing agents to the reagent. However, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to vary the concentration levels of the tissue factor and phosphatide in the reagent taught by Griffin et al to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed. It also would have been obvious to one of ordinary skill in the art to freeze-dry the reagent and add a buffer and stabilizing agents to the reagent taught by Griffin et al in order to preserve the reagent for an extended shelf life.

11. Claims 8-15, 23-29 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al in view of Gailani et al. For a teaching of McDonald et al and Gailani et al, see previous paragraphs in this Office action.

McDonald et al fail to teach that the capillary flow device can contain therein a reagent comprising tissue factor and a sulfatide. However, based upon the combination of McDonald et al and Gailani et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to include in the capillary flow device taught by McDonald et al the reagent taught by Gailani et al containing a tissue factor and a sulfatide, since McDonald et al disclose that the reagent in the capillary flow device must serve to activate the intrinsic coagulation pathway of blood, and Gailani et al teach that the combination of a tissue factor and a sulfatide serves to activate the intrinsic coagulation pathway of blood. It also would have been obvious to one of ordinary skill in the art to vary the concentration levels of the tissue factor and sulfatide in the reagent taught by Gailani et al to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed.

12. Claims 23-29 and 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonald et al in view of Griffin et al. For a teaching of McDonald et al and Griffin et al, see previous paragraphs in this Office action.

McDonald et al fail to teach that the capillary flow device can contain therein a reagent comprising tissue factor and either a phosphatide or a sulfatide. However, based upon the combination of McDonald et al and Griffin et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to include in the capillary flow device taught by

McDonald et al the reagent taught by Griffin et al containing a tissue factor and a phosphatide, since McDonald et al disclose that the reagent in the capillary flow device must serve to activate the intrinsic coagulation pathway of blood, and Griffin et al teach that the combination of a tissue factor and a phosphatide serves to activate the intrinsic coagulation pathway of blood. It also would have been obvious to one of ordinary skill in the art to vary the concentration levels of the tissue factor and phosphatide in the reagent taught by Griffin et al to the levels recited in the instant claims since concentration is a result effective variable that can be varied depending upon a desired intended use of the composition, and for optimization of a procedure being performed.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Please make note of the references cited previously on a PTO-892 form in the parent application: Griffin et al (US Patent no. 6,083,757) which corresponds to WO 96/15457; Hawkins et al, Brown, Brucato et al and Lee et al who teach of prothrombin time reagents containing tissue factor and phospholipids. Also, please make note of Bruegger (US Patent no. 6,699,718), which corresponds to the parent application.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 571-272-1266. The examiner can normally be reached on Monday-Wednesday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on 571-272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maureen M. Wallenhorst
Primary Examiner
Art Unit 1743

mmw

May 24, 2004

Maureen M. Wallenhorst
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